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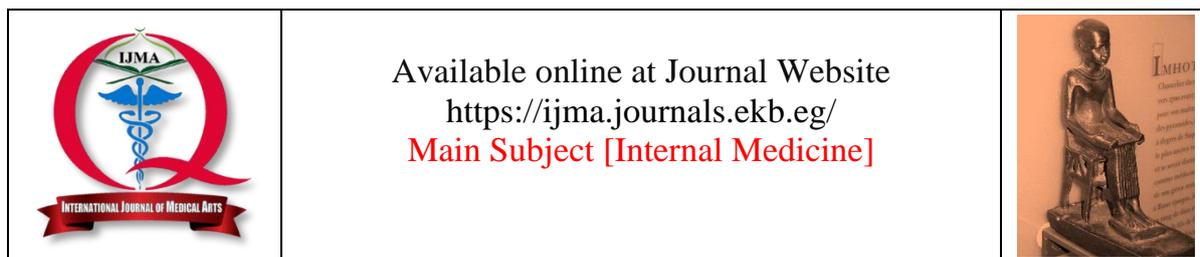


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## Original Article

# Retrospective Analysis on Efficacy and Safety of Glargine 100U and 300U in South Indian Type 2 Diabetes Population

Ganga Kiran<sup>1\*</sup>, Nadiminty Ganapathi Sastry<sup>2</sup>, G. Satish Kumar<sup>3</sup>, S. Dilipkumar<sup>4</sup>,  
 Lavanya Kalva<sup>5</sup>, G. Sireesha<sup>6</sup>

<sup>1</sup> Department of Internal Medicine and Diabetes, Dr. Kiran's Diabetes Care and Research Institute, Hyderabad, Telangana State 500034 India.

<sup>2</sup> Department of Internal Medicine and Diabetes, GVK Health Hub GVK Diabetes Care, Hyderabad, Telangana State 500034 India.

<sup>3</sup> Managing Director, JR'S Wellness Centre, Secunderabad, Telangana State 500034 India.

<sup>4</sup> Department of Internal Medicine and Diabetes, Dr. Dilip's Care Clinic and Archana Hospital, Hyderabad, Telangana State 500034 India.

<sup>5</sup> Department of Internal Medicine and Diabetes, Dr. Lavanya's Wellness Centre, Hyderabad, Telangana State 500034 India.

<sup>6</sup> Consultant at Sireesha Nursing Home, Chandha Nagar, Hyderabad, Telangana State 500034 India.

## ABSTRACT

### Article information

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\*Corresponding author

Email: [drangakiran185@gmail.com](mailto:drangakiran185@gmail.com)

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**Background:** The majority of individuals with type 2 diabetes [T2DM] are aware that in order to prevent microvascular diseases, they must maintain a healthy glycemic control. Since type 2 diabetes progresses with time, insulin therapy will eventually be required and beneficial for many patients, even though initial control can be obtained with lifestyle changes and oral antihyperglycemic medications. Insulin therapy, however, is linked to a higher frequency of hypoglycemia, which exposes patients to a variety of autonomic and neuroglycopenic symptoms.

**The aim of the work:** The aim of our study is to evaluate the effectiveness and safety of Insulin Glargine 100U and 300U in South Indian Type 2 Diabetes population.

**Patients and Methods:** Outpatients with adult type 2 diabetes who receive Glargine 100 U [Gla-100] as their basal insulin and outpatients with type 2 diabetes receiving Gla-300 treatment were included in the study population. For a span of two visits, the patients' diabetic therapy remained unchanged, with the exception of the Gla 100 dosage, before they were converted from Gla-100 to Gla-300 between July 2021 and June 2022. Retrospective enrolment in the current trial was made for patients who used Gla-100 continuously during the observational period without changing their other prescription regimen.

**Results:** The HbA1c levels were significantly decreased after switching [p<0.022]. The patients who remained taking Gla-100 at the same time period showed no change in their HbA1c levels. The patients' BMI values decreased significantly [p<0.023] and the patients who continued using Gla-100 showed no change in their BMI readings. Throughout the follow-up period, the rates of adverse events and hypoglycemia were unchanged.

**Conclusion:** Gla-100 to Gla-300 at the same dosage should be safe for people with Type 2 diabetes. This switch should aid in controlling body weight and blood sugar levels and is suitable for use in an outpatient setting.

**Keywords:** Type-2 Diabetes; Glycemic Control; Hypoglycemia; HbA1c Levels; Outpatients.



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## INTRODUCTION

Globally, the prevalence of diabetes mellitus [DM] has surged, resulting in a significant burden on society, the economy, and healthcare. Regardless of socioeconomic background or income level, diabetes mellitus [DM] is one of the illnesses that is causing significant changes in healthcare around the world. In comparison to 108 million in 1980, over 422 million people were expected to have diabetes mellitus [DM] in 2014, according to a 2016 World Health Organization forecast. In the adult population, from 4.7% to 8.5%, since 1980, the age-standardized prevalence of DM has almost doubled worldwide. This phenomenon can be attributed to the rise in risk factors linked with it, such being overweight or obese [1, 2]. The International Diabetes Federation estimates that 415 million people worldwide, or 8.8% of adults between the ages of 20 and 79, have diabetes, with over 75% of those affected living in low- and middle-income nations. If current patterns persist, 642 million individuals, or one adult in ten, will have diabetes by 2040 [3, 4].

Hyperglycemia is a defining feature of DM resulting from deficiencies in either insulin production, insulin function, or both. Patients with Type 1 Diabetes Mellitus [T1] typically develop the disease during childhood and require lifelong insulin supplementation to remain alive. Autoimmune destruction of the pancreatic  $\beta$ -cells is the main cause of T1DM [5, 6].

In type 2 [T2] diabetes mellitus, decreased insulin secretion and insulin resistance work together to cause elevated blood glucose [BG] levels. Oral Antihyperglycemic Drugs [OADs] are added as needed to maintain proper blood glucose control throughout the initial stages of treatment for type 2 diabetes [T2DM], which begins with dietary and activity changes [7, 8].

The epidemic of type 2 diabetes [T2DM], which impacts about 463 million individuals between the ages of 20 and 80, is still a serious global health concern despite seemingly attenuating in affluent nations [1]. T2DM is also a significant contributor to morbidity and premature death [Diabetes is responsible for around 11% of adult deaths] [1], with financial losses predicted to reach more than \$2 billion USD over the following ten years [2].

The majority of these expenses are associated with the disease's chronic consequences, which

are largely avoidable by attaining and maintaining glycemic goals, i.e., for most adult non-pregnant individuals, HbA1c less than 7% [53 mmol/mol] [3, 4].

A current recommendation for glucagon-like peptide 1 receptor agonists [GLP-1 RAs] is made by the American Diabetes Association [ADA] and the European Association for the Study of Diabetes [EASD] as the first injectable medication for those with type 2 diabetes [T2DM] because they may benefit cardio-vascular health [CV], reduce body weight and have a minimal chance of hypoglycemia [3, 4]. However, real-world observational studies have shown relatively low reported adherence to GLP-1RA [5] and as a result, there is a 0.5% difference between the HbA1c found in randomized controlled studies and data from the actual world [6]. Poor drug adherence appears to account for about 75% of the disparity.

However, insulin offers the benefit of dose-dependent blood glucose reduction, and with the right titration, HbA1c can be lowered to almost any target [3, 4, 7], with the danger of hypoglycemia serving as the only restriction. In fact, because T2DM is an evolving condition, insulin therapy will be necessary for many people at some time in order attain or maintain glycemic targets [8].

Furthermore, in patients with severe symptoms, high HbA1c, or fasting blood glucose [FBG], recent guidelines recommend starting insulin early [3, 4, 7]. However, a number of obstacles, including those pertaining to patients and doctors, frequently cause the start of insulin therapy to be delayed [9]. Enhancing glucose control may be possible by providing patients with enough education and encouraging them to self-monitor their blood sugar levels and adjust their insulin dosage.

The first option for starting insulin is typically basal insulin combined to metformin, other oral medications, or a GLP-1RA [3, 4] since compared to prandial or premix insulins, it reduces the chance of weight gain and hypoglycemia. The insulin dose should subsequently be titrated to reach the FBG target, which is normally 70–130 mg/dL. The starting dose is 10 international units QD, or 0.2 IU/kg/day. Compared to NPH insulin, an analog of basal insulin [glargine 100 U/mL [Gla-100], detemir] have a reduced chance of hypoglycemia, [mainly nocturnal]. However, when compared to Gla-100, the second-generation analogs of basal insulin [degludec and glargine 300 U/mL [Gla-300]], show an even reduced risk [10, 11].

Since 2015, the clinical use of basal insulin analog of the second generation, Gla-300, has been approved [12]. Its chemical structure and metabolism are identical to insulin Gla-100, but its concentration is three times higher [13]. As a result, this insulin preparation's pharmacokinetics and pharmacodynamics are altered, with an extended duration of activity [19-hour half-life and a duration of more than 24 hours overall], nearly non-peaking low intra-individual variability and action profile [14]. It was anticipated that these advantages will help diabetes patients with T1DM and T2DM clinically. Hence, the purpose of our study is to evaluate the effectiveness and safety of Insulin Glargine 100U and 300U in South Indian Type 2 Diabetes population.

## PATIENTS AND METHODS

### Study population

Adult type 2 diabetes outpatients treated with Gla-300 treatment for type 2 diabetic outpatients with Gla-100 as basal insulin were included in the study population. For two consultations in a row, the diabetic medications taken by the patients remained unchanged, with the exception of the Gla-100 dosage, before they were converted from Gla-100 to Gla-300 between July 2021 and June 2022. During the same period, the data of observation for patients who kept taking Gla-100 were collected to check the impact of the seasonal change in the HbA1c level. The American Diabetic Association standards served as the basis for the diagnosis of type 1 and type 2 diabetes. Retrospective enrolment in the current trial was made for patients who used Gla-100 continuously during the study period without changing their other medications. Gla-300 was administered to all patients at the same dose as was routine during outpatient visits. Insulin titration was performed following the basal insulin switch in accordance with the attending physician's guidelines. The Ethics Committee gave its clearance before the study could be carried out.

### Measurements

Five consecutive outpatient visits were used to collect the data. These visits comprised two pre-switch visits [Visits 1 and 2], a switch-initiation visit [Visit 3], and two post-switch visits [Visits 4 and 5]. From these visits, the following data were extracted: body weight [kg], systolic and diastolic blood pressure [mmHg], blood glucose levels [mg/dL], and HbA1c [%]. Furthermore, data on symptomatic hypoglycaemia episodes and

medication status were taken from the patients' medical records. The body mass index, or BMI, was calculated by dividing the height in meters by the square of the body weight in kilograms. Asymptomatic hypoglycaemia [ $<60\text{mg/dL}$ ] was possible since some of the patients had already received instruction on how to check their fasting blood glucose levels using a blood glucose monitor [self-monitored blood glucose, or SMBG] and report the data.

### Statistical analysis

The mean and standard deviation are used to express the data. Continuous variables were compared between patients who switched from Gla-100 to Gla-300 and those who continued on Gla-100 using age-adjusted analysis of variance [ANOVA]. Wilcoxon's rank sum test was used to compare the measurements obtained at Visit 3 with those obtained at Visits 1 and 2, as well as Visits 4 and 5, in the patients who had converted to Gla-300. The patients who continued to use Gla-100 had their measurements from Visit 3 compared to Visits 1, 2, 4, and 5 over the course of these five back-to-back visits. The following categories were created for the patients based on their HbA1c levels:  $<7.7$  [21], 7.7, 8.4 [25], and 8.5% [16]. We separated the HbA1c levels for the patients who kept on Gla-100 into the following categories: 7.2 [22], 7.2-7.6 [20], and 7.7% [18]. The following classifications were applied to the patients based on their BMI values:  $<23.2$  [21], 23.3- 26.7 [20], and 26.8  $\text{kg/m}^2$  [21]. We classified the BMI values of the patients who remained using Gla-100 into the following categories:  $<23.4$  [19], 23.5-26.5 [20], and  $\geq 26.6$   $\text{kg/m}^2$  [21]. Between the three groups, the variations in HbA1c were compared. Moreover, seven days of SMBG data were utilized to calculate the variations in the average fasting glucose level prior to and during the transition to evaluate the effects of basal insulin supply. P values less than 0.05 were considered statistically significant.

## RESULTS

### The clinical characteristics of study patients

Fifty-eight out of the 457 patients who underwent screening for Gla-100 prescription data were disqualified because they had been hospitalized at least once throughout the course of the five consecutive observation periods [for a variety of reasons]. Furthermore, 49 individuals were disqualified due to their usage of steroids, sporadic doctor visits, type 1 diabetes, or diabetes

other than type 2. Ultimately, Gla-100 and Gla-300 were administered to 150 patients with type 2 diabetes at the same dosage. Furthermore, we observed 200 individuals with type 2 diabetes who remained taking Gla-100 at the same dosage for three and six months, respectively, in an attempt to mitigate the effects of seasonal variations in the HbA1c level on study outcomes. Gla-100 was used twice in the treatment of a few patients. After moving from Gla-100 to Gla-300, the mean timing of the 12-month visit was  $5.9 \pm 1.8$  weeks following the baseline measurement. The mean time of the 12-month visit was  $4.8 \pm 1.6$  weeks after the baseline measurement for patients who continued to use Gla-100. Only 146 patients' medical records contained fasting glucose values.

### Changes in glycemetic control and insulin dose

After using Gla-300 for six months, the type 2 diabetes patients' HbA1c readings considerably changed; they went from  $8.04 \pm 0.94\%$  at 6 months to  $7.92 \pm 1.18\%$  at 12 months [ $p=0.022$  and  $p<0.001$ , respectively] [Figure 1]. Conversely, the HbA1c values of the type 2 diabetes patients who remained using Gla-100 did not alter in this way: they were  $7.47 \pm 0.81\%$  at six months and  $7.56 \pm 0.84\%$  at twelve months. At six months, the patients with type 2 diabetes received a dose of  $8.2 \pm 5.6$  U/day of Gla-300; at twelve months, the dose increased to  $8.6 \pm 6.3$  U/day. The dosages of Gla-100 were  $11.0 \pm 4.8$  U/day at 6 months and  $10.7 \pm 4.2$  U/day at 12 months for the type 2 patients who continued to use Gla-100. The patients with type 2 diabetes who transitioned to Gla-300 had bolus insulin dosages of  $16.1 \pm 6.2$  U/day at six months and  $15.7 \pm 5.5$  U/day at twelve months. After moving to Gla-300, the bolus insulin doses tended to go down, however the drop was not statistically significant. The

bolus insulin dosages of type 2 diabetic patients who kept using Gla-100 remained unchanged at  $15.3 \pm 5.4$  U/day at 6 months and  $15.4 \pm 5.2$  U/day at 12 months.

### BMI change

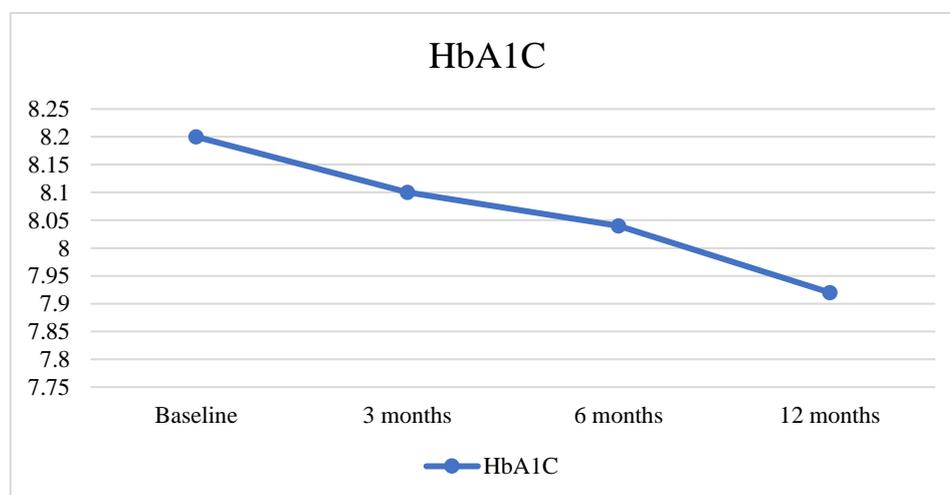
The patients' BMI values significantly dropped from  $25.3 \pm 4.0$  kg/m<sup>2</sup> at 6 months to  $25.1 \pm 3.8$  kg/m<sup>2</sup> at 12 months [ $p=0.023$ ] after switching to Gla-300 at 6 months. Conversely, the BMI values of the type 2 diabetic patients who kept using Gla-100 were unchanged at 6 months and 12 months, respectively, at  $25.4 \pm 3.8$  kg/m<sup>2</sup> and  $25.3 \pm 3.7$  kg/m<sup>2</sup>, respectively.

### The fasting and post prandial glucose data from the patients' SMBG records

The fasting SMBG information was taken from 146 patients' medical records. Among the patients, the mean fasting glucose levels dropped from  $154.2 \pm 34.6$  mg/dL to  $131.4 \pm 20.3$  mg/dL [ $p=0.07$ ], with no statistically significant difference seen. The patients' mean blood glucose levels after eating dropped from  $180.4 \pm 35.6$  mg/dl to  $160.8 \pm 20.2$  mg/dl [ $p=0.07$ ], with no statistically significant difference seen.

### Hypoglycemia and adverse events

During the follow-up period, no adverse events or occurrences of symptomatic hypoglycemia were noted in any of the patients' medical records. Nonetheless, during the follow-up period, there was only one instance of asymptomatic hypoglycemia noted in the medical records of the patients who remained using Gla-100. Furthermore, no injection-site reactions were recorded, and no participant left the research due to adverse events.



**Figure [1]:** Changes in glycemetic control after switching to Gla-300

## DISCUSSION

The effectiveness of Gla-100 in Asian patients with type 2 diabetes was investigated in this retrospective observational trial, along with the effects of moving from Gla-100 to the same dose of Gla-300. Consequently, we discovered that switching from Gla-100 to the same dose of Gla-300 in a clinical environment improved glycemic control and reduced body weight without causing any negative side effects. Comparing the overall number of type 2 diabetes patients who switched from Gla-100 to Gla-300 with those who stayed on Gla-100 for the entire six months, the EDITION JP2 trial [15] found that patients who made the switch to Gla-300 experienced an equal reduction in their HbA1c levels as those who continued to receive Gla-100. Furthermore, there were no variations in glycemic control between treatments. Furthermore, the trial's adjustments to the fasting glucose and HbA1c values were in line with treat-to-target based studies. However, a greater dosage of Gla-300 was required than Gla-100 to maintain the same level of glycemic control [15].

In our study, glycemic control and body weight improved when Gla-100 and Gla-300 were administered at the same dose, despite the fact that during the follow-up period, doctors did not often alter the insulin dosage that they administered to patients with type 2 diabetes. These disparities in the outcomes could be caused, at least in part, by variations in the injection tools used for Gla-300. Gla-300 was found to be helpful for patients with weaker hands [16] and to precisely provide the necessary insulin amount [13].

Given that other studies employing various devices did not demonstrate the same benefits, we conclude that even after the patients changed from Gla-100 to the same dose of Gla-300; this difference may have contributed to our study's improved glycemic control [15, 17]. Therefore, compared to Gla-100 [18, 19], the pharmacological profile of Gla-300 demonstrates pharmacokinetic and pharmaco-dynamic patterns that are consistent and extended, suggesting that it could be useful for these patients. The ideal candidates to move from Gla-100 to Gla-300 are those with high insulin sensitivity or whose glucose levels during fasting are under control by Gla-100 [i.e., patients with lean physical profiles].

In our trial, individuals with type 2 diabetes who changed to the same dosage of Gla-300 from Gla-100 experienced a reduction in body weight, which was in line with findings from earlier studies [15, 17].

Furthermore, even though the patients' self-monitored blood glucose [SMBG] records showed a drop-in mean fasting glucose, hypoglycaemic events—including asymptomatic ones—were uncommon in our study. Previous type 2 diabetes studies associated Gla-300 with a lower incidence of hypoglycemia as compared to Gla-100 [15, 17, 20].

Moreover, even though there was no statistical significance, the decrease in the frequency of asymptomatic hypoglycemia incidents has therapeutic significance as it suggests improved glucose regulation and a decreased necessity for superfluous meals that may result in weight gain. Further study is required to ascertain whether using Gla-300 as opposed to Gla-100 causes a favourable shift in body weight when hypoglycemia episodes diminish.

**Limitations:** Because of the limitations of this particular study, care must be taken in interpreting the findings. First of all, the study population was small because this study was observational and retrospective. To improve the credibility of our findings, more prospective studies with adequate statistical power conducted over longer research periods might be beneficial. Secondly, this research relied on real-world data without the need for titration. Needless to mention, enhancing the technology of insulin devices and modifying insulin dosages are essential for assisting individuals with type 2 diabetes in achieving appropriate glycemic control. Third, to lessen the impact of seasonal variation in the HbA1c level, we observed 200 patients in this trial who continued to take Gla-100 at the same dose for the same amount of time. Nonetheless, there were variations in a number of baseline characteristics among the individuals who went from Gla-100 to Gla-300, such as injection schedule and age. Therefore, we cannot completely rule out the chance that these variations had an impact on the study's findings. Fourth, when type 2 patients moved from Gla-100 to Gla-300, they might have encountered a placebo effect as a result of the therapy change, which could have contributed to the reported effects on the HbA1c level and body weight.

**Conclusion:** It should be safe for persons with Type 2 diabetes to switch from Gla-100 to the same dosage of Gla-300. This switch is appropriate for usage in the outpatient context and should help with both body weight control and glycemic control. It is necessary to conduct an additional prospective study in order to validate the results.

**Disclosure:** None to be disclosed

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